REMARKS

The Examiner provides a number of rejections which are listed here in the order in which they are addressed:

I. Claims 1-20 are rejected under 35 U.S.C. § 112 ¶ 2, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-20 are alleged as indefinite for functionality due to the phrase "...conjugating the fluorophore with an organic compound..." appearing in Claim 1 and the phrase "...reacting the organic compound and the fluorophore under covalent bond forming conditions..." appearing in Claim 2. As functional language, it is alleged that these phrases are impermissibly broader than the written description.

B. Claims 1-9 are alleged as indefinite by providing an impermissible overlapping range where a broad range or limitation is followed by a narrow range or limitation.

II. Claims 10-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mayer *et. al.*, U.S. Patent No. 4,647,675, in view of Arnost *et. al.* U.S. Patent No. 4,900,686, and Kang et. al. U.S. Patent No. 5,846,737.

I. Claims 1-20 Are Not Indefinite According To 35 U.S.C. § 112 ¶ 2

The Examiner has included Claims 1-20 in the rejection. This grouping is in error. A number of the claims do not have the alleged indefinite language. Moreover, functional claim language is not *per se* a basis for such a rejection.

A. The rejection is not appropriate for the group of claims

First, the Examiner is directed to the 2/26/01 Amendment in order to take note that Claim 2 was previously **cancelled**. Indeed, portions of Claim 2 were incorporated into Claim 1. Therefore, in so far as the Examiner's rejection is directed to Claim 2, it is moot.

Second, the Examiner is reminded that independent Claim 10 does not contain the phrases "...conjugating the fluorophore with an organic compound..." or "...reacting the

organic compound and the fluorophore under covalent bond forming conditions..." upon which the rejections to either Claim 1 or Claim 2 were initially based. This is because Claims 1-9 are method claims, and Claims 10-20 are claims to conjugates. The Applicant is forced to conclude that there are no specific rejections to Claims 10-20 based on 35 U.S.C § 112 ¶ 2. Even if the Examiner intended to assert such rejections, the Applicants' have not been provided with any specific issue(s) on which to respond.

B. Functional Claim Language Is Appropriate

The Applicants' reemphasize the discussion and argument presented in the 02/26/01 Amendment, and are not repeated herein in the interest of brevity. Those remarks and arguments are complemented with the following.

The Examiner states "Claims 1-2 are written in functional language, and therefore, broader than the enabling disclosure". *Office Action pg. 2 ¶ 2.* The Applicants' interpretation of this unsupported statement leads to the conclusion that the Examiner believes that **any claim in functional language** is automatically broader than the scope of the enabling disclosure and therefore precludes the use of any functional claim language. If this is true, the Examiner is creating limitations to patent claims that are inconsistent with current federal common law and PTO regulations. The Examiner is directed to *MPEP § 2173.05(g) Functional Limitations;*

> A functional limitation is an attempt to define something by what it does, rather than by what it is ... There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, **in and of itself**, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971) [emphasis added].

The Examiner's rejection **is based solely** on a functionality argument, and is therefore not in compliance with standard PTO practice and procedure. Similarly, the Examiner provides **no authoritative support** for the subsequent statement that "The claims must recite the reagents, the reaction times and conditions involve[d] in the processes". *Office Action pg. 2 ¶ 2.* The Applicants' are currently unaware of any Federal Circuit holdings or MPEP sections that require such specific limitations and information to reside within the body of claims. Prior to

any proceeding with any further rejections, the Applicants' request the Examiner provide unequivocal legal support for the above-quoted two statements.[1]

The Examiner's reliance on *In re Fressola* is misplaced. The Applicants' are not attempting to import the specification into the claims. However, the Applicants' are relying on the specification to provide support for the claims, which it clearly does.

Despite the above arguments, without acquiescing to the Examiners' arguments, but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, the Applicants' provide minor modifications to the second step of Claim 1. These changes do not modify the substantive nature of the embodiment claimed and are intended only to provide the Examiner with more clear and concise claim construction.

C. Claims 1-9 Have No Overlapping Ranges

The Examiner has also rejected Claims 1-9 on the basis that the broad recitation, "...Ra and Ra' are non-hydrogen substituents...", is followed by the (allegedly) more narrow range/limitation of, "...Ra' includes a group reactive to derivatization...". *Office Action pg 3 ln 11-15.* The Applicants' request the Examiner to review the 2/26/01 Amendment that clearly deletes, **by bracketing**, the phrase, "..., and Ra, includes a group reactive to derivatization...", from Claim 1. *2/26/01 Amendment pg 2, ln 19-20.* The Examiners' rejection of Claims 1-9 on this basis **is moot** and the Applicants' request withdrawal of this rejection basis.

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[1] "[T]he rule is that the burden of persuasion is on the PTO to show why the applicant is not entitled to a patent." *In re Epstein*, 31 USPQ2d 1817, 1825 (Fed. Cir. 1994) (Plager, J. joined by Cowen, J., concurring.)(citing to *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992) (Plager, J., concurring); *In re Warner*, 379 F.2d 1011, 1016, 154 USPQ 173, 177 (CCPA 1967), *cert. denied*, 389 U.S. 1057(1968)).

D. The 2/26/01 Amendment Deleted The Term "include"

The Examiner has provided a basis for ignoring the 2/26/01 Amendment due to the alleged continued use by the Applicants' of the claim term, "include";

> "Applicants' arguments filed 2/26/01 have been fully considered but they are not persuasive ... This is not persuasive because the phraseology starts with the term "include" which, under US patent practice, is a narrow term." *Office Action; pg 3 ln 16 - pg 4 ln 2.*

The Examiner is directed to claim amendments made to Claim 10 and Claim 12 in the 2/26/01 Amendment. The 2/26/01 Amendment clearly deletes, **by bracketing,** the term "includes" in both Claim 10 & Claim 12 and inserts "...represents a linker plus the.." and "...has...", respectively. *2/26/01 Amendment pg 4, ln 3-6.* The Examiner's rejection on this basis **is moot.** The Applicants' request the Examiner withdraw this rejection basis.

II. Claims 10-20 Are Not Obvious Under 35 U.S.C. § 103(a)

The Examiner alleges that Mayer *et. al.* teaches rhodamine dyes having formula 1 with several substituents. The Examiner admits that Mayer *et. al.* does not teach the conjugation of any compound to the rhodamine structure. The Examiner asserts that the gap left in Mayer *et. al.* is filled by; i) Arnost *et. al.* in that it teaches that ".. [rhodamine] dyes are commonly used as conjugates in biological diagnostic assays ...", and ii) Kang *et. al.* teaches "...rhodamine dyes ... conjugate[d to] ... peptides, proteins, nucleotides ..." and "... conjugation of rhodamine dyes to bacteria, virus, yeast and to immobilized solid or semi-solid support ..." *Office Action pg. 5.* The Examiner, in hindsight, concludes that these three references create and predict the Applicants' invention under a *prima facie* case of obviousness. The Applicants' disagree that this combination of references supply a proper *prima facie* case of obviousness and provide the argument below in support of this belief.

A. Mayer *et. al.* Is Non-Analogous Art

As a threshold issue, the Mayer reference is non-analogous art. Mayer *et. al.* does not even mention the word conjugation, conjugate, or any related discussion of possible adaptations or changes to the basic chemical formula. Mayers' *et. al.* only practical purpose is for dyeing various materials and use as printing inks. *Mayer et. al., col 2 ln 20-25.* Mayer *et. al.* does not consider modifying their invention to conjugate their basic structure with a

biological marker. "There is nothing in the prior art to lead a person of ordinary skill to the combination of the structures shown in these references to design [the invention] other than the hindsight knowledge of [the patentee's] construction." *Heidelberger Druckmaschinen v. Hantscho Commercial Products*, 30 USPQ2d 1377, 1380, 21 F.3d 1068 (Fed. Cir. 1994).

B. The Other References Teach Different Conjugates

The Examiner presents the disclosure of Arnost *et. al.* in an attempt to satisfy the deficiencies in the Mayer *et. al.* reference. The Applicants respectfully disagree and present the following argument.

The synthesis process defined by Arnost *et. al.* is silent concerning any teaching to control isomerization in order to create single isomer forms. To enable the synthesis of a single isomer conjugate the Applicants' teach the importance of providing a blocking capability via the N-R_a substituent; "One function of the R_a substituent is to **block lactam ring formation...**" *Applicants' Specification pg 5 ln 7 [emphasis added].* The specification underscores the advantage of single isomer forms:

> Because compounds of the invention preferably possess functional groups linked through the 3-position carboxyl group, the linkage converts the 3-position carboxylate to a non-acidic function (e.g. amide), which confers better stability to derivatives such as phosphoramidites. By virtue of doing the chemistry through the 3-position carboxyl group, the inventive dyes and labeling derivatives are single isomer forms, unlike compounds which require purification from mixtures of 5- and 6-position carboxyrhodamines before preparing oligonucleotide labeling reagents.

Applicants' Specification pg. 5 ln 20-27.

By contrast, Arnost *et. al.* teaches conjugating only nitrogen-based lactam ring structures at the 3-position carboxylate (see Arnost *et. al.* structures: XI, XV, XVII, XVIII, XXI, XXV, XXXI, and XXXII). The Arnost *et. al.* structures require two amino cyclizations (Z_q-N[R_1]-W_p and Y_n-N[R]-X_m). *Arnost et. al. col. 19 ln 5-18.* Arnost *et. al.* defines each amino cyclization arm (*i.e.*, Z_q, W_p, Y_n, and X_m) to consist of an aliphatic chain ranging between 1-4 carbons. Arnost *et. al.* does not contemplate any non-cyclized substitutions containing solely hydrogen, alkyl, carboxylalkyl, aminoalkyl, alkylether, alkylthioether, halogen or alkoxy.

Without acquiescing to the Examiners' argument but to further the prosecution and better define one embodiment, and hereby expressly reserving the right ot prosecute the

original (or similar) claims, Applicants have amended Claim 10 to underscore the absence of lactam ring formation.

The Kang *et. al.* also does not satisfy the deficiencies of the Mayer reference. The Kang reference teaches conjugation of various compounds to **sulfated substituents** at either the 1 or 3 position of a rhodamine general structure; "The dye conjugates of the present invention are all derivatives of tetramethyl-or tetraethylsulforhodamine sulfonyl chloride." *Kang et. al., col. 3 ln 56-58.* Sulfonyl reactive groups are not mentioned nor contemplated in either Mayer *et. al.* or Arnost *et. al.*. A result of this lack of teaching or suggestion there is no motivation from either of the two latter references to support any combination with Kang *et. al.* As discussed below, Kang *et. al.* points out significant differences between the use of sulforhodamine and other structures described in the art:

> The additional spacer in the sulforhodamine-peptide conjugates of the instant invention places the fluorophore further away from the peptide binding site, which may result in improved binding of the peptide probes to its receptor relative to the same peptide labeled with SBSC, which lacks the spacer. *Kang et. al. col. 5 ln 50-58.*

Therefore, Kang *et. al.* does not contemplate any of the methods or results disclosed by the Applicants'. Moreover, there **cannot** be any motivation to combine the teachings with Mayer *et. al.*, or Arnost *et. al.* since Kang teaches linkers that are (allegedly) superior.

CONCLUSION

The Applicants believe that upon entering into the record the previous changes made in the 2/26/01 Amendment many of the rejections made by the Examiner are rendered moot. In addition, it is submitted that the arguments and claim modifications set forth in the present Amendment traverse the Examiners' rejections. Therefore, the Applicants' request that all grounds for rejection be withdrawn. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 617-252-3353.

Dated: October 23, 2001

Peter G. Carroll
Registration No. 32,837
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220 Montgomery Street, Suite 2200
San Francisco, California 94104

APPENDIX I
MARKED-UP VERSION OF REWRITTEN CLAIMS
PURSUANT TO 37 CFR § 1.121 (c)(1)(ii)

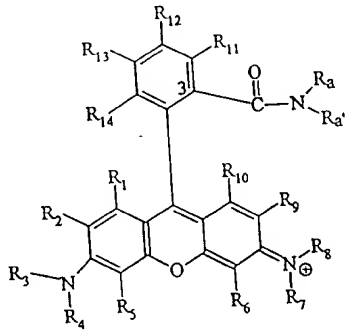
The Following is a version of the claims pursuant to 37 C.F.R. § 1.121(c)(1)(ii) with markings showing the changes made herein to the previous version of record of the claims.

Please amend the following claims:

1. A method of labeling an organic compound for fluorescent detection, comprising:

providing a fluorophore having the structure illustrated by Formula A

FORMULA A



where R_1 and R_{10} taken alone are hydrogen or halogen; R_2, R_5, R_6 and R_9 taken alone are hydrogen, alkyl, carboxyalkyl, aminoalkyl, alkylether, alkylthioether, halogen or alkoxy; R_3, R_4, R_7 and R_8 taken alone are hydrogen, and substituted or unsubstituted alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl; R_2 and R_3 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 2′ carbon to the nitrogen attached to the 3′ carbon; R_9 and R_8 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 7′ carbon to the nitrogen attached to the 6′ carbon; R_4 and R_5 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 4′ carbon to the nitrogen attached to the 3′ carbon; R_6 and R_7 taken together are alkyl, each having from 2 to 5 carbon

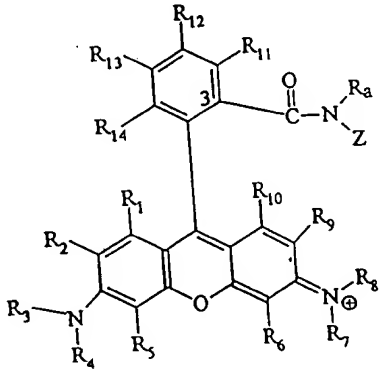
atoms connecting the 5′ carbon to the nitrogen attached to the 6′ carbon; R_3 and R_4 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 3′ carbon; R_7 and R_8 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 6′ carbon; R_{11}, R_{12}, R_{13}, and R_{14} are each hydrogen or halogen, where R_a and $R_{a'}$ are non-hydrogen substituents, wherein R_a confers resistance to lactam ring formation; and,

conjugating the fluorophore with an organic compound at the Ra' group [to be labeled] under covalent bond forming conditions, [the conjugating through the Ra' group of the fluorophore,] wherein the resultant conjugate is a single isomer being fluorescent upon excitation with light of a determinable wavelength.

10. A fluorescent conjugate comprising:

a conjugated substance and a fluorophore, the conjugated substance being an amino acid, peptide, protein, nucleotide, oligonucleotide, or nucleic acid to which is attached one or more fluorophores, the fluorescent conjugate having the structure illustrated by Formula 1

FORMULA 1



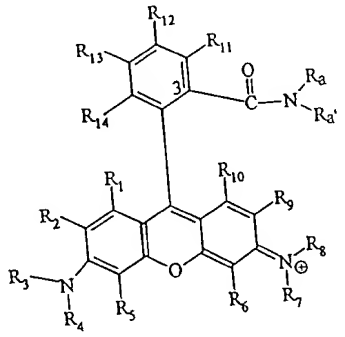
where R_1 and R_{10} taken alone are hydrogen or halogen; R_2, R_5, R_6 and R_9 taken alone are hydrogen, alkyl, carboxyalkyl, aminoalkyl, alkylether, alkylthioether, halogen or alkoxy; R_3, R_4, R_7 and R_8 taken alone are hydrogen, and substituted or unsubstituted alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl; R_2 and R_3 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 2′ carbon to the nitrogen attached to the 3′ carbon; R_9 and R_8 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 7′ carbon to the nitrogen attached to the 6′ carbon; R_4 and R_5 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 4′ carbon to the nitrogen attached to the 3′ carbon; R_6 and R_7 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 5′ carbon to the nitrogen attached to the 6′ carbon; R_3 and R_4 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 3′ carbon; R_7 and R_8 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 6′ carbon; R_{11}, R_{12}, R_{13}, and R_{14} are each hydrogen or halogen, where R_a is an alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl, or arylalkyl having from 1 to 10 carbon atoms, and Z represents a linker plus the conjugated substance, wherein said conjugated substance lacks a lactam ring.

APPENDIX II
CLEAN VERSION OF THE ENTIRE SET OF PENDING CLAIMS
PURSUANT TO 37 CFR § 1.121 (c)(3)

1. A method of labeling an organic compound for fluorescent detection, comprising:

providing a fluorophore having the structure illustrated by Formula A

FORMULA A



where R_1 and R_{10} taken alone are hydrogen or halogen; R_2, R_5, R_6 and R_9 taken alone are hydrogen, alkyl, carboxyalkyl, aminoalkyl, alkylether, alkylthioether, halogen or alkoxy; R_3, R_4, R_7 and R_8 taken alone are hydrogen, and substituted or unsubstituted alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl; R_2 and R_3 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 2′ carbon to the nitrogen attached to the 3′ carbon; R_9 and R_8 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 7′ carbon to the nitrogen attached to the 6′ carbon; R_4 and R_5 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 4′ carbon to the nitrogen attached to the 3′ carbon; R_6 and R_7 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 5′ carbon to the nitrogen attached to the 6′ carbon; R_3 and R_4 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen

attached to the 3′ carbon; R_7 and R_8 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 6′ carbon; R_{11}, R_{12}, R_{13}, and R_{14} are each hydrogen or halogen, where R_a and $R_{a'}$ are non-hydrogen substituents, wherein R_a confers resistance to lactam ring formation; and,

conjugating the fluorophore with an organic compound to be labeled under covalent bond forming conditions, the conjugating through the $R_{a'}$ group of the fluorophore, the resultant conjugate being fluorescent upon excitation with light of a determinable wavelength.

3. The method as in claim 2 wherein the organic compound is a biomolecule.

4. The method as in claim 3 wherein the biomolecule is an amino acid, a peptide, a protein, a nucleotide, an oligonucleotide, or a nucleic acid.

5. The method as in claim 3 wherein the biomolecule is attached to a solid support.

6. The method as in claim 3 wherein the biomolecule is an oligonucleotide and the fluorophore is attached via a phosphoramidite at the 5′ end in the conjugate.

7. The method as in claim 5 wherein the biomolecule is an oligonucleotide and the fluorophore is attached at the 3′ end in the conjugate.

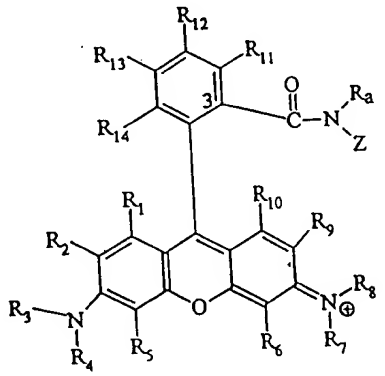
8. The method as in claim 3 wherein the biomolecule is an amino acid, a peptide or a protein, and the fluorophore is attached at an amine or sulfhydryl in the conjugate.

9. The method as in claim 3 wherein the biomolecule is part of a cell surface membrane or of a viral coat.

10. A fluorescent conjugate comprising:

a conjugated substance and a fluorophore, the conjugated substance being an amino acid, peptide, protein, nucleotide, oligonucleotide, or nucleic acid to which is attached one or more fluorophores, the fluorescent conjugate having the structure illustrated by Formula 1

FORMULA 1



where R_1 and R_{10} taken alone are hydrogen or halogen; R_2, R_5, R_6 and R_9 taken alone are hydrogen, alkyl, carboxyalkyl, aminoalkyl, alkylether, alkylthioether, halogen or alkoxy; R_3, R_4, R_7 and R_8 taken alone are hydrogen, and substituted or unsubstituted alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl; R_2 and R_3 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 2′ carbon to the nitrogen attached to the 3′ carbon; R_9 and R_8 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 7′ carbon to the nitrogen attached to the 6′ carbon; R_4 and R_5 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 4′ carbon to the nitrogen attached to the 3′ carbon; R_6 and R_7 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 5′ carbon to the nitrogen attached to the 6′ carbon; R_3 and R_4 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 3′ carbon; R_7 and R_8 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from

the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 6′ carbon; R_{11}, R_{12}, R_{13}, and R_{14} are each hydrogen or halogen, where R_a is an alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl, or arylalkyl having from 1 to 10 carbon atoms, and Z represents a linker plus the conjugated substance, wherein said conjugated substance lacks a lactam ring.

11. The conjugate as in claim 10 wherein the conjugated substance is bound to the fluorophore through an amide, ester, ether, disulfide, or thioether linkage.

12. The conjugate as in claim 10 wherein the linkage between the fluorophore and conjugated substance has a phosphate ester.

13. The fluorescent conjugate as in claim 10 wherein the conjugated substance is attached to a solid support.

14. The fluorescent conjugate as in claim 13 wherein the solid support is controlled pore glass.

15. The fluorescent conjugate as in claim 13 wherein the solid support is a polymer support.

16. The fluorescent conjugate as in claim 10 wherein the conjugated substance is part of a cell membrane.

17. The fluorescent conjugate as in claim 10 wherein the conjugated substance is part of a viral coat.

18. The fluorescent conjugate as in claim 10 wherein the fluorophore is derived from tetramethylrhodamine.

19. The fluorescent conjugate as in claim 10 wherein the fluorophore is derived from rhodamine 101.

20. The fluorescent conjugate as in claim 10 wherein the fluorophore is derived from rhodamine B.